(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 February 2004 (05.02.2004)

PCT

(10) International Publication Number
WO 2004/011625 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number: PCT/US2003/024065

(22) International Filing Date: 31 July 2003 (31.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/400,276 | 31 July 2002 (31.07.2002) | US |
| 60/400,253 | 31 July 2002 (31.07.2002) | US |
| 60/400,250 | 31 July 2002 (31.07.2002) | US |
| 60/400,249 | 31 July 2002 (31.07.2002) | US |

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF SOUTHERN CALIFORNIA** [US/US]; 3716 South Hope Street, Suite 313, Los Angeles, CA 90007-4344 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LENZ, Heinz-Josef** [DE/US]; 2753 Winrock Avenue, Altadena, CA 91001 (US). **STOEHLMACHER, Jan** [DE/US]; 146 Melrose Avenue, Monrovia, CA 91016 (US). **PARK, David, (Jong-Han)** [US/US]; 17800 East Colima Road, #350, Rowland Heights, CA 91748 (US).

(74) Agent: **KONSKI, Antoinette, K.**; Bingham McCutchen LLP, Three Embarcadero Center, Suite 1800, San Francisco, CA 94111-4067 (US).

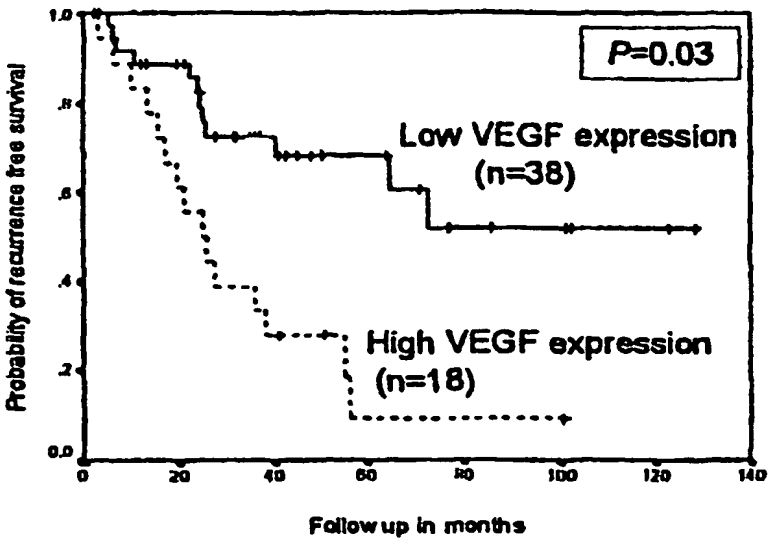
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: POLYMORPHISMS FOR PREDICTING DISEASE AND TREATMENT OUTCOME




(57) Abstract: The invention provides compositions and methods for determining the increased risk for recurrence of certain cancers and the likelihood of successful treatment with one or both of chemotherapy and radiation therapy. The methods comprising determining the type of genomic polymorphism present in a predetermined region of the gene of interest isolated from the subject or patient. Also provided are nucleic acid probes and kits for determining a patient's cancer risk and treatment response.

WO 2004/011625 A2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 February 2004 (05.02.2004)

PCT

(10) International Publication Number
WO 2004/011625 A3

(51) International Patent Classification[7]: C12Q 1/68, C07H 21/02, 21/04

(21) International Application Number: PCT/US2003/024065

(22) International Filing Date: 31 July 2003 (31.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/400,276 | 31 July 2002 (31.07.2002) | US |
| 60/400,253 | 31 July 2002 (31.07.2002) | US |
| 60/400,250 | 31 July 2002 (31.07.2002) | US |
| 60/400,249 | 31 July 2002 (31.07.2002) | US |

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF SOUTHERN CALIFORNIA** [US/US]; 3716 South Hope Street, Suite 313, Los Angeles, CA 90007-4344 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LENZ, Heinz-Josef** [DE/US]; 2753 Winrock Avenue, Altadena, CA 91001 (US). **STOEHLMACHER, Jan** [DE/US]; 146 Melrose Avenue, Monrovia, CA 91016 (US). **PARK, David, (Jong-Han)** [US/US]; 17800 East Colima Road, #350, Rowland Heights, CA 91748 (US).

(74) Agent: **KONSKI, Antoinette, K.**; Bingham McCutchen LLP, Three Embarcadero Center, Suite 1800, San Francisco, CA 94111-4067 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 11 November 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: POLYMORPHISMS FOR PREDICTING DISEASE AND TREATMENT OUTCOME

(57) Abstract: The invention provides compositions and methods for determining the increased risk for recurrence of certain cancers and the likelihood of successful treatment with one or both of chemotherapy and radiation therapy. The methods comprising determining the type of genomic polymorphism present in a predetermined region of the gene of interest isolated from the subject or patient. Also provided are nucleic acid probes and kits for determining a patient's cancer risk and treatment response.

WO 2004/011625 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/24065

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC(7) : C12Q 1/68; C07H 21/02, 21/04
US CL : 435/6; 536/23.1, 23.5
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6; 536/23.1, 23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,705,336 A (REED et al) 06 January 1998 (06.01.1998), column 2, lines 3-12, column 3, lines 45-47 and column 8. | 1-6, 10 and 11 |
| X | SWEENEY et al. Association between survival after treatment for breast cancer and glutathione S-transferase P1 Ile105Val polymorphism. Cancer Research. 15 October 2000, Vol. 60, pages 5621-5624, see especially page 5623. | 1-5, 10 and 11 |
| X | WEI et al. Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. Journal of Clinical Investigations. August 1996, Vol. 98, No. 3, pages 610-615, especially page 615. | 1-5 |
| X --- Y | EDLER et al. Thymidylate synthase expression: an independent prognostic factor for local recurrence, distant metastasis, disease-free and overall survival in rectal cancer. Clinical Cancer Research. April 2000, Vol. 6, pages 1378-1384, especially page 1382. | 1-4, 6, 10, 11 ---------- 5 |
| X --- Y | LEICHMAN et al. Quantitation of intratumoral thymidylate synthase expression predicts for disseminated colorectal cancer response and resistance to protracted-infusion fluorouracil and weekly leucovorin. Journal of Clinical Oncology. October 1997, Vol. 15, No. 10, pages 3223-3229, especially pages 3227-3228. | 1-4, 6, 10, 11 ---------- 5 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
06 July 2004 (06.07.2004)

Date of mailing of the international search report
27 SEP 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Carla Myers
Telephone No. 571-272-0747

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

PCT/US03/24065

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | HORIE et al. Functional analysis and DNA polymorphism of hte tandemly repeated sequences in the 5'-terminal regulatory region of hte human gene for thymidylate synthase. Cell Structure and Function. 1995, Vol. 20, pages 191-197, especially page 195. | 5 |

# INTERNATIONAL SEARCH REPORT

PCT/US03/24065

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid

Group 1, claims 1-6, drawn to a method for selecting a therapeutic regimen for treating a cancer in a patient, wherein the method comprises screening a suitable cell or tissue isolated form said patient for a genomic polymorphism or phenotype that is correlated to treatment outcome of the cancer.

Group 2, claims 7-9, drawn to a method for reducing chemically induced neurotoxicity associated with chemotherapy in a patient comprising administering an effective amount of COX-2 inhibitor.

Group 3, claims 10-11, a method for determining if a patient is more likely to experience tumor recurrence comprising determining the level of expression of TS, DPD, ERCC1 or VEGF. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding technical feature among the claimed inventions. While Groups I-III are each directed to methods associated with cancer, each group has a different special technical feature not shared by the remaining groups. In particular, Group I is directed to methods for selecting a therapeutic regimen. The methods of Group I require screening a cell or tissue sample for the presence of a genomic polymorphism or genotype that is associated with treatment outcome. The special technical feature of group I is the association between polymorphisms or genotypes and the selection of therapy. The methods of groups II and III do not require detecting a polymorphism or genotype as a means for selecting a therapy. Group II is directed to methods for reducing chemically induced neurotoxicity associated with cancer and has the special technical feature of administering a COX-2 inhibitor. The methods of Groups I and III do not share this special technical feature. Group III is drawn to methods for determining if a patient is more likely to experience tumor recurrence. The special technical feature of Group III is the determination of expression levels as predictive of risk for tumor recurrence. The methods of Groups I and II do not require determining expression levels of TS, DPD, ERCC1 or VEGF as a means for predicting risk for tumor recurrence.

**Continuation of B. FIELDS SEARCHED Item 3:**

DIALOG: MEDLINE, CA, BIOSIS, EMBASE, SCISEARCH; WEST: US, EP, JP, WO Patents

search terms: TS, thymidylate synthase., ERCC1, VEGF, ERC2, XRCC-1, glutathione transferase, GSTP1, EGFR, metalloproteinase, MMP1, MMP3, IL-1, interleukin 8, DPD, pyrimidine dehydrogenase, CXC chemokine, therapy, chemotherapy, treatment, drug, cancer, tumor, carcinoma

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/24065

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-6, 10 and 11

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.